REMARKS

Claim 9 is pending in the instant application.

The Examiner has maintained the rejection of claim 9 under 35 U.S.C. § 103 as being unpatentable over Bowes et al. (Neurology 1995) in view of Mulligan et al. (Amer. Pathol. 1993) or Panes (Amer. Physiol. 1995), and Muzykantov et al. (BBA 1986), Runge et al. or Torchilin.

Reconsideration and withdrawal of this rejection is respectfully requested in light of the following remarks.

Arguments presented by Applicants in the last response were not deemed convincing by the Examiner.

In particular, the Examiner suggests that Applicants argued the references individually and not their combination. It is respectfully pointed out that Applicants' discussed the deficiencies in each secondary reference individually because the combination with Bowes et al. is improper.

At page 4 of the Office Action, the Examiner cites In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981) and MPEP 2145 as teaching that the test of obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and not is it that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the reference

would have suggested to those of ordinary skill in the art. Applicants respectfully direct the Examiner to the paragraph in MPEP 2145 following the In re Keller citation wherein it is specifically stated:

> [h]owever, the claimed combination cannot change the principle of operation of the primary reference or render the reference inoperable for its intended purpose.

As pointed out in Applicant's last response filed in December of 2004, the suggestion by the Examiner to modify the teachings of the primary reference of Bowes et al., which requires separate administration of anti-ICAM-1 antibody and tPA at different times, specifically a two hour separation in administration of the antibody and the anti-thrombotic agent, would change the principle of operation of the primary reference. In fact, the Examiner's proposed modification will very likely render the Bowes reference inoperable for its intended purpose, namely preventing neurologic damage occurring in the reperfusion phase of ischemic-reperfusion injury. Support for this suggested modification of simultaneous administration of the antibody and tPA as a conjugate rendering the Bowes et al. reference inoperable for its intended purposes is set forth in Bowes et al. Exp. Neurology 1993 119:215-219.

The most recent Office Action from the Examiner does not address this argument.

However, MPEP 2143.01 clearly states that if the proposed modification would render the prior art invention unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. Thus, since there is no motivation or suggestion to make the proposed modifications to Bowes and, as discussed in detail in the December 2004 response, each of the secondary references fails to suggest or teach all of the claim limitations, Applicants respectfully disagree with the Examiner's suggestion at page 4 of this instant Office Action that any burden has shifted to Applicants with respect to this rejection since no *prima facie* case of obviousness has been established.

Further, at page 5 of the instant Office Action, the Examiner has cited a new prior art reference of Almenar-Queralt et al. (Am. J. Pathol. 1995 147(5):1278-88) suggested by the Examiner to be an evidentiary reference supporting the Examiner's position that "it has been known prior to Applicant filing date that the accumulation of anti-ICAM-1 mAb 1A29 taught by in the pulmonary vasculature Mulligan et al. is due to non-internalizable characteri[s]tic of the anti-ICAM-1 antibody." It is respectfully pointed out, however, Almenar-Queralt performed their experiments in cytokine-activated endothelial cells. It is well-established that cytokines profoundly alter

cellular physiology, including expression, shedding and internalization of cell adhesion molecules. Mulligan et al. also performed their tests in cytokine-challenged animals. Accordingly, teachings of these references, cited by the Examiner to be predictive of non-internalizability of anti-ICAM targeted conjugated *in vivo* are irrelevant to obviousness of the instant invention which targets, not cytokine-challenged cells but rather the luminal surface of the pulmonary endothelium of an animal.

Further, the paper of Mulligan et al. utilized endothelial cells from a different species and a different anti-ICAM antibody as compared to Almenar-Queralt et al. References such as Kluger et al. (J. Immunol. 1997 158(2):887-96 demonstrate that internalization of even the same antibody directed to a cell adhesion molecule is greatly dependent on the type and location of endothelial cells in the vasculature even within the same species. Furthermore, monoclonal antibodies directed against different epitopes of the same membrane protein have been shown to differ dramatically in their internalization rate. See for example, Muzykantov et al. Drug Delivery 1998 5:197-206. In fact, there are a number of references teachings internalization of an agent via ICAM-1. See for example Staunton et al. J. Immunol. 1992 148(10):3271-4; Grunert et al. Med. Microbiol. Immunol. 1997 186(1):1-9; Yusuf-

Makagiansar et al. Pharm. Res. 2001 18(3):329-35; and Mastrobattista et al. Biochim Biophys. Acta 1999 1419(2):353-63. Thus, the skilled artisan would not make the Examiner's suggested connection of studies by Mulligan describing pulmonary accumulation of one anti-ICAM antibody in one animal species with work of Almenar-Queralt et al. in a different species and different vascular source in light of all the other prior art in this area. Clearly in no way was non-internalizability of anti-ICAM1 antibodies conjugated to an anti-thrombotic agent obvious over these two references, or more properly when viewed in light of the prior art as a whole.

It is therefore respectfully requested that reconsideration of this rejection be given in light of the above remarks and that this rejection under 35 U.S.C. 103 be withdrawn.

Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record.

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Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

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